**FGFR1** loss-of-function mutations of in three Japanese patients with isolated hypogonadotropic hypogonadism and split hand/foot malformation

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**METHODS**

**OBJECTIVES**
Background: Heterozygous loss-of-function mutations of FGFR1 are known to cause Kallmann syndrome (KS) and isolated hypogonadotropic hypogonadism (IHH). Furthermore, recent studies have also indicated that heterozygous loss-of-function mutations may lead to IHH and split hand/foot malformation (SHFM).

Objective and hypotheses: The objective of this study was to examine FGFR1 in three Japanese patients with IHH and SHFM.

**METHODS**

**Method:** This study consisted of three Japanese patients (cases 1–3) with IHH and SHFM. Case 1 was a 3-month-old boy with microcephaly, low serum LH (<0.1 mL/mL) and testosterone (<0.03 ng/mL) at mini-puberty, and right split hand. Case 2 was a 17-year-old boy with no pubertal development, low serum LH (<0.1 mL/mL) and testosterone (<0.03 ng/mL), and bilateral split hands and feet. Case 3 was a 34-year-old female with primary amenorrhea, low serum LH (0.4 mL/mL) and E2 (<10 pg/mL), and left split hand. We performed direct sequencing for FGFR1 coding regions and their flanking splice sites, luciferase analysis for missense mutations, and RT-PCR based sequence analysis and in silico analysis for a splice donor site mutation.

**RESULTS**

Direct sequencing identified two heterozygous missense mutations (a previously reported p.G97S in case 1 and a novel p.R742T in case 2) and a novel heterozygous splice donor site mutation (IVS12+1G>T in case 3). The two missense mutations had drastically reduced luciferase activities, without a dominant negative effect. The splice donor site mutation was found to have yielded a small amount of mRNA skipping exon 12 (p.Ser512_Gly553delinsCys), and was predicted to have produced two aberrant mRNAs that satisfy the condition for nonsense-mediated mRNA decay, by using an alternative splice donor site (p.G553fsX628) and by escaping splicing at the IVS12 exon boundary

**CONCLUSIONS**
The results provide further support for the notion that heterozygous loss-of-function mutations of FGFR1 cause IHH with SHFM.

**REFERENCES**


**Table**

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**References**